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Management of advanced nodal disease in patients treated with primary chemoradiotherapy

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Abstract

Purpose of review:

The management of advanced nodal disease in patients treated with chemoradiotherapy has been a controversial topic for many years. New data has recently been reported, including the results of a multicenter randomized trial making this review timely.

Recent findings:

The PET NECK trial showed that PET CT surveillance is as effective as planned neck dissection in terms of overall survival, but results in much fewer neck dissections, less complications and is more cost effective. Cost effectiveness data from a single centre study demonstrated that strategies that include PET CT were more effective than CT-alone guided strategies.

Summary: There is now level I evidence to support image-guided surveillance strategies as the standard of care for advanced nodal disease in patients treated with primary chemoradiotherapy.

KEY WORDS: neck dissection, Positron emission tomography, chemoradiotherapy

Introduction

The management of advanced nodal (N2-N3) disease in patients with head neck cancer treated with primary chemoradiotherapy (CRT) continues to vary widely between institutions and countries. Whilst many in the US adopt image-guided, response-based strategies, a significant proportion in other countries still practice planned neck dissection. For example, up to 48% of patients with oropharyngeal cancer in the UK were found to have neck dissection as their first treatment in a recent national audit.⁽¹⁾ In France, 35% of head neck clinicians surveyed reported that they commonly or routinely performing neck dissection before CRT⁽²⁾.

These variations in practice are the mainly due to contradicting evidence and the lack of randomized comparative studies. This article reviews the most recent data in the field:

Literature supporting planned neck dissection

Previous retrospective studies showed that 40% of neck dissections post chemoradiotherapy contained persistent disease on histopathological examination.⁽³⁾ There was also level 3 evidence from retrospective studies

demonstrating a significant survival advantage in favour of planned neck dissection, compared to CRT alone.^(4, 5) As a result, traditionally, these patients have been treated with a 'planned' neck dissection, either before or after chemoradiotherapy, despite the risk of significant morbidity and even mortality.⁽⁶⁾

Literature supporting image-guided surveillance

As the quality of cross-sectional imaging improved over the past two decades, studies consistently reported low rates of recurrence following image-guided surveillance. For example, Thariat et al reported rates of recurrence of 4% in the 30% of subjects showing complete response on CT scans.⁽²⁾ However those patients who showed partial response or equivocal complete response on CT scanning had high recurrence rates of 37% and 32% if they did not have a neck dissection. Such data has stimulated the increasing adoption of response-based approaches following CRT.

The efficacy of FDG PET-CT in this indication

The advent of Positron Emission Tomography (PET), using ^{[18]F}-fluorodeoxyglucose [FDG PET], is a form of functional imaging which identifies abnormal metabolic activity of tumour cells and specifically increased glucose metabolism in tumour cells. It potentially conferred advantages over other cross-sectional imaging modalities in identifying residual disease following CRT. More recently, combined PET-CT scanners have been developed. PET-CT localizes abnormal functional metabolic

activity of tumour cells, and also shows structural abnormalities, such as nodal enlargement. There have been two notable meta-analyses assessing the diagnostic performance of FDG-PET and FDG PET-CT in this indication. These have included mainly, single hospital, retrospective and prospective studies. The meta-analyses demonstrated high negative predictive values of 94.5- 96% with positive predictive values of approximately 50% for FDG PET and FDG PET-CT scanning following chemoradiotherapy [CRT].^(7, 8) FDG PET and PET-CT scanning may therefore be able to identify even more patients with complete response following chemoradiotherapy, resulting in fewer neck dissections.⁽⁹⁾

Till recently, there was no prospective multi-centre, randomised evidence. However, the PET NECK study has recently reported⁽¹⁰⁾. The study recruited 564 patients, randomized into either a planned neck dissection arm or a PETCT active surveillance arm. PET CT was non-inferior in terms of overall survival (i.e. there was no survival detriment for not having or delaying neck dissection) and only 19% of patients had a neck dissection in the PET CT arm, with less complications and the same overall quality of life. The active surveillance PET-CT arm was significantly more cost-effective than the planned neck dissection arm.

HPV disease and equivocal PET-CT results

In our PET NECK study, patients with equivocal responses on FDG PET-CT scanning received a neck dissection. Our definition of equivocal responses

included those patients with residual masses but no FDG uptake or those patients with mild FDG uptake regardless of nodal size.

Patients who had demonstrated equivocal complete responses on CT scanning after chemoradiotherapy had a high nodal recurrence rate of 37%, similar to that of patients who showed partial or no response.⁽²⁾

Recent reports suggest HPV+ nodal disease may take longer to reduce in size⁽¹¹⁾, and therefore may present with equivocal FDG PET-CT scans (in particular with enlarged nodes on the CT scan component, but without FDG avidity) at the 12 week post CRT assessment. Other recent reports suggest that patients who show no FDG uptake had very low recurrence rates, especially if they had HPV + disease (93%)^(9, 12). Therefore, patients with HPV+ disease who show enlarged nodes but no FDG uptake after CRT may be considered for close surveillance with serial frequent scans. Patients with FDG uptake should continue to have a neck dissection, especially if they have HPV negative or high risk HPV-positive disease. The role of ultrasound guided biopsies and diffusion weighted MRI should be evaluated in this group of patients.

FDG PET-CT versus CT-guided surveillance

A prospective study by Moeller et al reported that the diagnostic accuracy of FDG PET-CT was only better than CT in high-risk patients who have HPV negative disease, non-oro-pharyngeal primaries or who have a smoking or

alcohol history. There was no benefit seen in low risk patients who are non-smokers with HPV+ oropharyngeal primaries⁽¹³⁾ . The authors acknowledge that the study limited for several reasons. Firstly, it was performed in high-throughput cancer institution where the proportion of high risk patients and radiotherapy non-responders may be greater than in other treatment settings. Secondly, FDG PET-CT nodal response was assessed at mean of 8 weeks [range 5-12 weeks] following treatment, which may not be the optimal timing for FDG PET-CT after RT⁽⁷⁾. And finally, histopathology of post CRT neck dissection was used as evidence of persistent disease, which overestimates tumour persistence^(9, 14).

Indeed, other studies that compared FDG PET-CT to CT have reported much higher efficacy of FDG PET-CT compared to CT in HPV+ patients. Mak et al reported that FDG PET/PET-CT scanning at a mean time of 12 weeks [range 8-16 weeks] following treatment was significantly more accurate at predicting complete response (90%) compared to contrasted CT assessment (46%), and especially for HPV+ patients (93% vs 50%)⁽¹²⁾. In one of the largest studies to date which specifically considered FDG PET-CT response in HPV+ oropharyngeal cancer, FDG PET-CT at 12 weeks post CRT demonstrated high NPV for loco-regional failure though with disappointing PPV and sensitivity ⁽¹⁵⁾.

Pryor et al demonstrated that surveillance strategies utilising FDG PET-CT were more cost effective than CT guided surveillance alone, regardless of the HPV status of the patient. Furthermore, that study showed that combined

strategies using CT followed by FDG PET-CT in non-responders were only slightly more cost effective than FDG PET - CT alone, and were very sensitive to changes in circumstances⁽¹⁴⁾.

As yet, independent validation of CT scan-driven response systems or comparison with PET-CT –driven systems in *multicenter, randomised* settings have not been published. Even if further studies shows FDG PET-CT is of limited value in HPV+ patients, it should perhaps be noted that in many countries, this low risk HPV+ constitutes only a minority of patients, and FDG PET-CT would still have a important role in the majority of patients.

Conclusions

There now appears to be strong, level 1 evidence to support FDG PET-CT - guided surveillance for patients with advanced nodal disease treated with CRT. There is also a large body of retrospective evidence to support CT guided surveillance. However, the available evidence favours FDG PET-CT guided policies over CT-only guided regimens on the basis of cost-effectiveness.

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Conflicts of interest

A has received honoraria from Merck and MSD, as well as academic grants from GSK, SPMSD and Astra Zeneca. The remaining authors have no conflicts of interest.

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